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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 05/21/2008

SUBJECT: **Difenconozole; Section 18 Emergency Exemption for Use of Difenoconazole on Cucurbit Vegetables (Crop Group 9); Human-Health Risk Assessment.**

PC Code:	128847	**DP No.:**	351241
Decision No.:	391843	**Registration No.:**	08GA01
Petition No.:	NA	**Regulatory Action:**	Section 18
Risk Assessment Type:	Single Chemical/Aggregate	**Case No.:**	NA
TXR No.:	NA	**CAS No.:**	119446-68-3
MRID No.:	NA	**40 CFR**	§180.475

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Background:

The Georgia Department of Agriculture has submitted a request for a Section 18 Emergency Exemption for the use of difenoconazole (1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1*H*-1,2,4-triazole) on cucurbits for the control of gummy stem blight (*Didymella bryoniae*). This is the first Section 18 request for this use. A summary of the estimated human-health risk resulting from the requested use of difenoconazole is provided in this document.

NOTE: HED recently completed a Section 3 risk assessment for the use of difenoconazole on a variety of commodities (Memo, M. Sahafeyan, *et al.*, 11/09/07, D246591). This document contains only those aspects of the risk assessment which are affected by the addition of these new uses of difenoconazole on cucurbit vegetables.

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Triazoles Dietary Exposure and Risk Assessments: The aggregate dietary (food + water) acute and chronic dietary exposure analyses for difenoconazole metabolites 1,2,4- triazole (1,2,4-T) and triazole alanine (TA) and triazole acetic acid (TAA) from all registered and proposed triazole-based fungicide uses already include exposure to cucurbits at higher exposure levels by other triazole-based fungicides and are not of concern (Memo, M. Doherty, DP#322238, 11/01/2005). In the case of the cucurbit crop group, the difenoconazole residue of 1.0 ppm translates to higher exposures to triazole metabolites than from other triazole-based fungicide uses on cucurbits that are already covered in the last dietary assessment for triazoles. Although, the aggregate dietary risk assessment for triazoles is being updated to include this level of use on cucurbits, it can be said with a fairly high degree of certainty that adding these Section 18 uses will not result in any risk issues for the triazole metabolites from HED's perspective (Memo, 5/7/08, M. Sahafeyan, 08CA12, DP# 351715).

Conclusions/Recommendations: Provided the petitioner submits a revised proposed label, HED concludes that the toxicological, residue chemistry, dietary-exposure, and occupational/residential exposure assessments support the granting of the subject Section 18 Emergency Exemption and a time-limited tolerance for residues of difenoconazole [1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1*H*-1,2,4-triazole] in or on vegetables, cucurbits, group 9 at 1.0 ppm.

Proposed Application Scenarios

Proposed Use: The GA Department of Agriculture is requesting application of Inspire Super MP (EPA Reg. No. 100-1262) to cucurbit vegetables for the control of gummy stem blight (*Didymella bryoniae*). Inspire contains 23.2% (by volume) difenoconazole as the active ingredient (ai). Up to 4 applications may be made at 0.10 pounds (lb) ai per acre (A). The maximum seasonal use rate is 28 ounces (oz) of product/A or 0.41 lb ai/A. The use directions specify the product is to be applied when conditions are conducive for disease. A retreatment interval (RTI) of 7 to 10 days and a pre-harvest interval (PHI) of 1 day are proposed. The label specifies that difenoconazole is to be applied as a tank mix with Vangard WG containing cyprodinil as the ai. The use of cyprodinil on cucurbit vegetables is not discussed in this document.

HED's Conclusions: The submitted use directions are adequate to allow evaluation of the residue data relative to the proposed use. However, the label contains a typographical error that needs to be corrected. Under the "Specific Use Restrictions", the maximum seasonal rate is specified as 28 oz of Inspire/A/season or "0.45 lb ai/A/season". This is incorrect as 28 oz of product equals 0.41 lb ai. Additionally, the following rotational crop restriction is required: "Rotate only to crops for which difenoconazole is registered." **A revised label is required.**

Residue Chemistry Considerations

Nature of the Residue in Plants and Livestock: The nature of the residue in plants is understood based on acceptable plant metabolism studies with canola, grape, potato, tomato, wheat, and

ruminants. Based upon a review of the previously-submitted metabolism data for difenoconazole, HED concludes the residue of concern for both tolerance setting and risk assessment for crops is difenoconazole *per se*. Additionally, HED concludes the residue of concern for both tolerance setting and risk assessment for livestock tissues are difenoconazole and its metabolite CGA 205375.

Nature of the Residue - Rotational Crops: The nature of the residue in rotational crops is not adequately understood. In the absence of data, the following rotational crop restriction is required: "rotate only to crops for which difenoconazole is registered."

Analytical Enforcement Method: The current enforcement method for plant commodities, Method AG-575B, determines residues of difenoconazole by gas chromatography (GC) with a nitrogen-phosphorus detector (NPD). For the purposes of this Section 18 only, Method AG-575B is adequate for enforcement of tolerances for residues of difenoconazole in/on cucurbit vegetables (group 9).

Magnitude of the Residue in Cucurbit vegetables (group 9):

Reference: 46950234.de1.doc

For the purposes of this Section 18 Emergency Exemption only, HED is translating data from fruiting vegetables to cucurbit vegetables. Data for twenty field trials (11 tomato, 6 bell pepper, and 3 non-bell pepper) conducted with difenoconazole have been submitted. At each trial location, there was one untreated and one treated plot. The treated plots received four foliar broadcast applications of difenoconazole at a nominal application rate of 0.115 lb ai/A, for a total seasonal application rate of 0.460 lb ai/A/season. At each trial location, one untreated control and two treated samples were collected immediately following the last application (after the spray had dried).

Tomato and pepper samples were analyzed for residues of difenoconazole using GC/NPD Method AG-575B. The maximum difenoconazole residues in/on samples harvested at the 0-day PHI were 0.41 ppm for tomatoes, 0.20 ppm for bell peppers, and 0.29 ppm for non-bell peppers.

For the purposes of this Section 18 request only, HED concludes a time-limited tolerance of 1.0 ppm for residues of difenoconazole in/on cucurbits is adequate.

Dietary Risks (Food and Water Only)

Reference: Memo, in preparation, M. Sahafeyan, D352204

Acute and Chronic Dietary-Exposure Results and Characterization

Aggregate (food + water) acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID™, ver. 2.03) model. This model uses food consumption data from the United States Department of

Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII; 1994-1996 and 1998). The acute and chronic analyses assumed tolerance-level residues and 100% CT for all registered and proposed crops. Tolerance-level residues were also assumed for all livestock tissues in this assessment. Experimental processing factors were used for apple juice (0.04x), potato chips (0.5x), potato granules/flakes (0.5x), sugar beet molasses (0.6x), sugar beet refined sugar (0.6x), tomato paste (1.6x), and tomato puree (0.5x); DEEM™ (ver. 7.76) default processing factors were assumed (when appropriate) for other processed commodities.

The drinking water values used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (Memo, I. Maher, 19-JUN-2007; DP# 333319).

Acute Dietary (food + water) Exposure and Risk Assessment

The resulting acute dietary (food + water) exposure estimates are not of concern to HED (<100% of the acute population-adjusted dose (aPAD)) at the 95th percentile of the exposure distribution for the U.S. general population (2.9% aPAD) and all population subgroups; the most highly exposed population subgroup was all-infants <1 year old at 9.0% aPAD (see Table 2).

Chronic Dietary (food + water) Exposure and Risk Assessment

The resulting chronic dietary (food + water) exposure estimates are not of concern to HED (<100% of the chronic population-adjusted dose (cPAD)) for the U.S. general population (23% cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 65% cPAD (see Table 2).

Cancer Dietary Exposure and Risk Assessment

A separate cancer dietary assessment was not conducted for difenoconazole because the cancer no-observable-adverse-effect-level (NOAEL) is higher than the chronic reference dose (RfD); therefore, the chronic dietary risk estimate is protective of carcinogenic effects.

Table 1. Summary of Dietary (Food + Drinking Water) Exposure and Risk for Difenoconazole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.007277	2.9	0.002265	23	0.002265	23
All Infants (< 1 year old)	**0.022518**	**9.0**	0.005586	56	N/A	N/A
Children 1-2 years old	0.019060	7.6	**0.006516**	**65**		
Children 3-5 years old	0.016481	6.6	0.005547	56		
Children 6-12 years old	0.009954	4.0	0.003287	33		
Youth 13-19 years old	0.004989	2.0	0.001663	17		
Adults 20-49 years old	0.004768	1.9	0.001632	16		
Adults 50+ years old	0.005685	2.3	0.001880	19		
Females 13-49 years old	0.004915	2.0	0.001637	16		

Residential Exposure

Difenoconazole is registered for residential uses and HED believes residential pesticide handlers will be exposed to difenoconazole for short-term duration (1 to 30 days) only.

The dermal and inhalation (short-term) residential exposure was assessed for "homeowners" mixer/loader/applicator wearing short pants and short-sleeved shirts as well as shoes plus socks using garden hose-end sprayer, "pump-up" compressed air sprayer, and backpack sprayer. A margin of exposure (MOE) of 100 is adequate to protect residential pesticide handlers from exposures to difenoconazole. MOEs are >100; therefore, are not of concern. The lowest MOE (230) and highest exposure was for dermal exposure using a "pump-up" compressed air sprayer.

Aggregate Risk

Including all existing and proposed uses, human-health risk assessments have been conducted for the following exposure scenarios: acute and chronic dietary exposures (food + water) and residential short-term exposure (dermal + inhalation). **The aggregate exposure and risk estimates are not of concern.**

Short-Term Aggregate Risk Assessment: Since a common endpoint has been identified for assessment of short-term oral, dermal, and inhalation exposures (changes in body weights and body-weight gains) the short-term aggregate risk assessment considered exposure from food,

water, and residential sources. Since the doses corresponding to the identified oral, dermal, and inhalation endpoints were different but the level of concern for all three routes of exposure are identical, the short-term aggregate exposures were calculated using the 1÷MOE approach. HED combines chronic dietary (food and water) exposure estimates with residential exposure estimates when conducting short-term aggregate risk assessments. Short-term exposure has been defined as from 1- 30 days and HED has concluded that chronic dietary exposure estimates will more accurately reflect actual dietary exposure over these time periods than will high-end acute-dietary exposures. The proposed residential scenarios result in exposure to only adults. Therefore, short-term aggregate assessments were not conducted for infants and children. Table 2 is a summary of the short-term aggregate exposures and risk estimates. Since the aggregate MOEs are ≥170, short-term aggregate exposure to difenoconazole is not of concern.

Table 2. Short-Term Aggregate Exposure and Risk Estimates.

Population	Target Aggregate MOE[1]	dietary MOE[2]	dermal + inhalation MOE[3]	agg. MOE (dietary and residential)[4]
Youth 13-19 years old	100	750	230	180
Adults 20-49 years old		770		180
Adults 50+ years old		660		170
Females 13-49 years old		760		180

[1] Total uncertainty factor for all routes of exposure is 100x; therefore, the target MOE is 100.
[2] Dietary MOE = short-term incidental oral NOAEL ÷ chronic dietary exposure.
[3] Dermal MOE = short-term dermal NOAEL ÷(dermal + inhalation residential exposure) (see text).
[4] Aggregate MOE (dietary and residential) = $1 \div ((1 \div MOE_{dietary}) + (1 \div MOE_{dermal}) + (1 \div MOE_{inhalation}))$.

Occupational Exposure

For a complete assessment of occupational exposure and risk from the use of difenoconazole in/on cucurbits see : DIFENOCONAZOLE – Occupational Exposure/Risk Assessment for a Georgia Section 18 Request to Use Difenoconazole on Cantaloupes, Watermelons and Cucumbers, 4/16/08, M.I. Dow, DP #: 351381.

Occupational Pesticide Handler Exposure:

A MOE of 100 is adequate to protect occupational pesticide handlers from exposures to difenoconazole. Provided handlers wear protective gloves as specified on the label, all MOEs are greater than 100. Therefore the proposed uses are not of concern to HED.

Post-Application Exposure To Agricultural Workers:

A MOE of 100 is adequate to protect agricultural workers from post-application exposures. The MOE is greater than 100 therefore the proposed uses are not of concern to HED.

Restricted Entry Interval (REI):

Difenoconazole is classified in acute Toxicity Category III for acute dermal toxicity and primary eye irritation. It is classified in Toxicity Category IV for acute inhalation toxicity and primary skin irritation. It is negative as a dermal sensitizer. Therefore, the interim worker protection standard (WPS) REI of 12 hours is adequate to protect agricultural workers from a most of post-application exposures to difenoconazole. The draft Inspire® label lists the REI as 12 hours.

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Registration 08GA01
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